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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,723	NAKAGAWARA, AKIRA	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The preliminary amendment filed 2/28/02 has been entered. Claims 6-12 were added. Claims 1-12 are pending and examined herein.

2. Applicant is advised that should claim 1 be found allowable, claim 6 will be objected to under 37 CFR 1.75 as being a duplicate thereof. Applicant is advised that should claim 2 be found allowable, claim 9 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, these claims are identical.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claims 1 and 6 are identical, and they are indefinite because it is not clear what a "homozygous deletion region" is. For example, it is not clear if it is a nucleic acid that has a deletion or an nucleic acid consisting of a region that is deleted in chromosome 1 or is it the absence of a portion of a nucleic acid or is it merely the knowledge that a deletion exists in a nucleic acid, i.e. the information? Neither the claims nor the specification set forth what a "deletion region" is in the context of these claims. If a deletion region is a nucleic acid, it is still not clear if the claim to "a homozygous deletion region" is a claim to a nucleic acid that is the portion of chromosome 1p36 that is deleted or if the claim is to a version of a chromosome that has a deletion. Does the fact that the deletion region is characterized as a "homozygous" deletion region mean that in order to meet the limitations of the claims two chromosomes must be present? There is no clear language in the claim that indicates if the intention of the claim is to be drawn using open or closed claim language. Furthermore, it is not clear if the language requiring that the deletion region is "present in common" means that the subject matter of the claim has the region present or absent, and if the "deletion region" is present, does that mean that the entire chromosome is in tact, at least at position 1p36? That is, it is not clear what it means for a deletion region to be "present in common." First, it is not clear what it means for the deletion region to be "present" and second, it is not clear what the "in common" is referring to. Also, it is unclear what the "deletion region" has to be "in common" to- all human neuroblatoma cells and cell lines, more than one human neuroblastoma cell or cell line, or some other combination of possibilities. Furthermore, the phrase "on the short arm of chromosome 1 of human neuroblastoma" is unclear, because human neuroblastoma is a disease and does not itself

have chromosomes. Claims 2-5 and 7-12 all depend from either claim 1 or claim 6 and are indefinite over these same recitations.

Claims 2 and 9 are indefinite over the recitation "the SP6 end" or "the T7 end" of the particularly recited clones. PAC clones are circular molecules which contain both an SP6 promoter and a T7 promoter. The orientation of these promoters when the clone cut by a restriction enzyme and made linear is entirely dependent on where the clone is cut to make it linear. Thus, since there is not a singular end in a circular clone, the phrases "the SP6 end" and "the T7 end" lack proper antecedent basis in the claims and render the claims indefinite. Claims 3, 4, 5, 10, and 11 depend from claim 2 or claim 9 and are indefinite over the same recitation.

Claims 2 and 9 are further indefinite over the recitation of "the PAC clone dJ1028013," "the PAC clone dJ371E1," and "the PAC clone dJ142A6" because reference to these arbitrary designations fails to set forth the metes and bounds of the invention as the designations of the PAC clones are not known in the art, nor does the specification give a definition of the metes and bounds of these clones. Claims 3, 4, 5, 10, and 11 depend from claim 2 or claim 9 and are indefinite over the same recitation.

Claims 2 and 9 are further indefinite over the recitation "the primer set D1S2736" because there is no antecedent basis in the claim for this phrase. "D1S2736" appears to be referring to a microsattellite marker, but the specification does not define the marker or give its sequence. Therefore, in the context of this claim D1S2376 is an arbitrary identifier whose meaning is unknown. Presumably, this marker could be amplified with any number of primer pairs selected from within the marker, and so there is not just one primer pair that is "the primer set" associated with this marker. The specification teaches one such primer set in Table 2 of the

specification but it is not clear if when applicant refers to "the" primer set if applicant is referring to the particular SEQ ID NO's in Table 2 or if applicant is referring to any primer set that could be used to detect this marker. Claims 3, 4, 5, 10, and 11 depend from claim 2 or claim 9 and are indefinite over the same recitation.

Claims 3, 8, and 10 are further indefinite over the recitation "the primer set SGC30343 and D1S2736." This phrase lacks proper antecedent basis in the claims as neither the claims nor the specification previously recite such a primer set, and it is not clear from the specification or the claims which primers such a set would require or contain. "D1S2736" and "SGC-30343" appear to be referring to a microsattellite markers, but the specification does not define the markers or give their sequences. Therefore, in the context of this claim D1S2376 and SGC-30343 are an arbitrary identifier whose meanings are unknown. The specification at page 21, table 2, teaches a primer set referred to as "SGC-30343" which consists of instant SEQ ID NO: 32 and 39 and amplifies a product "near 129 bp." The specification, at page 31, in table 6 recites a primer set that is referred to as "D1S2736" which consists of instant SEQ ID NO: 18 and SEQ ID NO: 43. It is not clear if the set referred to in claims 3, 8, and 10 is referring specifically to these sets, or if these arbitrary identifiers are referring to some other primer set that could be used to identify the referenced markers. Further, it is not clear from the claims or the specification, however, if the set referred to in claims 3, 8, and 10 would contain the forward primer from SGC30343 and the reverse primer from D1S2736, or if the set would be required to contain all four primers or if any combination of primers from the two sets would suffice to make up the primer set SGC30343 and D1S2736. Furthermore, even if the primer set were clear, it is not clear what it means for the region to be "characterized by being further defined" by the primer

set. It is not clear if that means the region must comprise the segments of chromosome 1 amplified by the primer set or if the regions delineated by the primer sets are the end points of the region, for example.

Claim Rejections - 35 USC § 112- Deposit Rules

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2, 3, 4, 5, 7, 9, 10, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to claims 2, 3, 4, 5, 9, 10 and 11, it is apparent that the DNA clones identified as PAC clones dJ1028O13 and dJ142A6 are required to practice the claimed invention. As such, they must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise known and readily available to the public. There is no showing in the specification that these clones are not readily known and available to the public. If it is not so obtainable or available, the requirements of 35 USC 112, first paragraph may be satisfied by an enabling deposit of the PAC clones. PAC clone DJ371E1, which is also recited in these claims is not included in the deposit requirement because the entire sequence of this clone is give in the specification (Example 8, SEQ ID NO: 60-64).

With regard to claims 4, 5, 7, 11, and 12, it is apparent that the DNA cell lines identified as NB-1 and MASS-NB-SCH-1 are required to practice the claimed invention. As such, they

must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise known and readily available to the public. The specification indicates that these were obtained as gifts from other researchers, but does not provide a showing in the specification that these cell lines are readily known and available to the public. If they are not so obtainable or available, the requirements of 35 USC 112, first paragraph may be satisfied by an enabling deposit of the cell lines. It is noted that the prior art contains reference to both of these cell lines, however, it has not been established that these cell lines were known and **readily available** to the public, as is required for adequate written description.

The teachings of the specification are not sufficient assurance that all of the conditions of 37 CFR 1.801-1.809 have been met. If a deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released upon issuance of a patent would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that :

(a) during pendancy of the application, accession to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Amendment of the specification to recite the date of the deposit and the proper name of the deposited plasmid (i.e. the ATCC accession number) is also required to satisfy the deposit requirement.

Claim Rejections - 35 USC § 112, Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are indefinite but can be interpreted to be drawn to a nucleic acid that comprises a homozygous deletion region that is present in common at position 1p36, that is, position 36 on the short arm of chromosome 1. Claims 1 and 6 provide that the deletion region is "present in common at position 36 on the short arm of chromosome 1 of human neuroblastoma." Claims 2 and 9 delineate end points for the deletion region based on locations of PAC clones and

a microsattelite marker. Claims 3, 8, and 10 recite that the region is characterized by being further defined by a primer set SGC30343 and D1S2736. Claims 4, 5, 7, 11, and 12 designate that the region is deleted in NB-1 and MASS-NB-SCH-1 cell lines.

The claims do not set forth a structure for the claimed subject matter. There is no teaching of a nucleic acid sequence, or even clear boundaries for the claimed subject matter. First, the claims appear to encompass a "homozygous deletion region" from any species of animal. The claims encompass any deleted region on present within position 36 of the short arm of chromosome 1, including for example, single base pair deletions as well as deletions of the entire arm of the chromosome or of the entire chromosome itself. The 1p36 region of human chromosome 1 contains hundreds of thousands of bases, and a wide variety of deletions are possible within this region, and applicant has not provided any clear elucidation of even a single region, let alone any way of identifying all of the possible deletions within this region. Further, of all of those possible deletions applicant has not provided relevant characteristics to identify those that are homozygous and "present in common" on the chromosomes of any or all human neuroblastomas.

The specification does not provide a clear elucidation of even a single homozygous deletion region present in cells from human neuroblastoma. The specification teaches a putative deletion from two particular neuroblastoma cell lines region that is delineated, for example, in figure 9, but even within the region delineated as a "deletion region" in these two cell lines the specification teaches that the marker D1S244 is present (specification, page 19, lines 18-22). At best, this deletion region was shown to be present in two of 27 neuroblastoma cell lines. The specification has not described a homozygous deletion in any primary neuroblastoma. The

specification does describe the nucleotide sequence of four PAC clones that are designated to be within this region (SEQ ID NO: 60-88, collectively, see Example 8). Applicant is clearly in possession of nucleic acids consisting of these nucleic acids. It is noteworthy, that while these nucleic acids cover a larger portion of the putative deletion region, they do not cover at least 20 kb of the region, see Figure 9.

Furthermore, with regard to the claims that recite primers within particular markers, three is no written description provided for the sequence of the markers, and thus, primer pairs other than those specifically disclosed in the specification that are within these markers are not described. A review of the prior art of record and a search by the examiner was unable to identify the sequences of the markers recited in the claims.

With regard to the written description, all of these claims encompass nucleic acid sequences different from those disclosed in the specific SEQ ID No:s as the claims encompass any number of possible deletion regions within chromosome 1p36.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of the claimed deletion regions, other than those nucleic acids whose sequences are given in the specification.

10. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The claims are drawn to "A homozygous deletion region is present in common" at position 1p36, position 36 on the short arm of chromosome 1, of human neuroblastoma. It is not clear from the claims or the specification the precise subject matter of the claims. Claims 1 and 6 provide that the deletion region is "present in common at position 36 on the short arm of chromosome 1 of human neuroblastoma." Claims 2 and 9 delineate end points for the deletion region based on locations of PAC clones and a microsattelite marker. Claims 3, 8, and 10 recite that the region is characterized by being further defined by the primer set SGC30343 and D1S2736. Claims 4, 5, 7, 11, and 12 designate that the region is deleted in NB-1 and MASS-NB-SCH-1 cell lines.

Due to the indefinite nature of the claims, the precise nature of the invention is unclear, but could encompass any number of possible nucleic acids or information. This rejection is

directed towards interpretations of the claims which require a "homozygous" deletion that is present "in common" in the cells all human neuroblastomas.

Scope of the claims

The claims are very broad in nature. The encompass any deletion region in human neuroblastoma on chromosome 1p36, including possible single base pair deletions, loss of entire chromosomes, loss of hundreds of thousands of base pairs. Further, due to the indefinite nature of the claims, the claims could encompass intact chromosomes (which comprise the deletion region) or could encompass a probe which comprises only the putative deleted region. A variety of art rejections are set forth herein to elucidate this point. The claims do require that the deletion region be a "homozygous region" present "in common" in on chromosme 1p30 "of human neuroblastoma."

State of the Art

The prior art teaches a consensus deletion region in neuroblastomas that includes 1p36.1-1p36.2 (see, for example Schwab *et al.*, as cited in IDS, p. 212, second column). Martinsson *et al.* (European Journal of Cancer, Vol. 33, No. 12, pp. 1997-2001, 1997) further pinpointed this region to a 25 cM region within chromosome region 1p36 (see Figure 1), and demonstrate that D1S244, among other markers is deleted within this region, shows loss of heterozygosity in tumor samples (Table 1). Grenet *et al.* (cited in the IDS as Kidd *et al.*) also teach a region that is hemizygously deleted in neuroblastoma cell lines on human chromosome 1p36. Hiraiwa *et al.* (as cited in the IDS) teach the MASS-NB-SCH-1 cell line and teach that a deletion of chromosome 1p for one chromosome (p. 2040 and Figure 9). There is no teaching in the prior art of a homozygous deletion in neuroblastoma cell lines or primary tumor samples.

Further, at the time the invention was made, it was known in the prior art that observations of genetic status in cancer cell lines are frequently not observable in primary tumor tissues. For example, Sidransky *et al.* (US 5856094) teach that although the rate of a homozygous deletion of P16 ranged from 40-60% of breast cancer cell lines, neither homozygous deletions nor point mutations are typically observed in primary breast carcinomas (Col. 2, lines 9-14). The suitability of cell lines in general as models for primary tumors is also questioned in the prior art. For example, Dermer (Bio/Technology, Vol. 12, March 1994, p. 320) teaches that "[w]hen a normal or malignant body cell survives a crisis period and adapts to immortal life in culture, it takes an evolutionary-type step that enables the new cell line to thrive in its artificial environment...Yet normal or malignant cells in vivo are not like that. This means that cell lines are really a new life form on Earth, neither human nor animal. Evidence of the contradictions between life on the bottom of the lab dish and in the body has been in the scientific literature for more than 30 years, evidence that has been systematically ignored by the cancer establishment (first column)."

Teachings in the Specification

The specification discusses an attempt to delineate a "homozygous" deletion region that was common to two of twenty-seven neuroblastoma cell lines. However, the data and statements provided in the specification appear to contradict one another, especially with regard to a marker identified as D1S244. The specification teaches that this marker was present in the two key cell lines but then also indicates that this marker is included within the deletion region referred to as the "homozygous deletion region." The specification does not teach a homozygous deletion region in any additional cell lines, or in any primary tumor samples. Further, while the claims

encompass any number of possible homozygous deletions in a chromosomal region that is millions of base pairs long, the specification discusses only one possible deletion that is about 500 base pairs long. A detailed analysis of the examples follows.

Working Examples

The specification teaches the screening of twenty-seven neuroblastoma cell lines for deletion in the 1p36 region of human chromosome 1 using a primer pair referred to as D1S548 and a primer pair referred to as D1S244 (p. 16-17). These primer pairs amplify portions of the 1p36.23-31 region, and are identified in the instant specification as SEQ ID NO: 25 and SEQ ID NO: 28 (D1S548) and SEQ ID NO: 26 an SEQ ID NO: 7 (D1S244) (p. 17). An amplification product for the D1S548 primer pair was observed in all of the cell lines. No amplification product was observed for the D1S244 region in 25 of the 27 cell lines. The specification teaches that only cell lines NB-1 and MASS-NB-SCH-1 showed an amplification product with the second primer pair which amplified the marker D1S244 (p. 19, lines 18-22).

Example 4 of the specification teaches further PCR amplification of genomic DNA from cell lines NB-1 and MASS-NB-SCH-1 with five additional primer pairs known to amplify portions of the 1p23.23-31 region (p. 19-22). No amplification was observed using any of these primer pairs in these cell lines. Figure 8 shows how the primer pairs are situated across the putative "deletion region." It is noteworthy that primer pair D1S244, which produced an amplification product in these two cell lines, is situated between primer pairs PGD and D1S2736 both of which did not produce amplification products in these two cell lines. However, based on the amplifications from this example, the specification concludes that in these two cell lines the deletion region encompasses all of the chromosome from the region amplified by primer pair

SGC30343 to the region amplified by primer pair D1S2736, inclusive of the region shown in the previous example (D1S244) to be present in these two cell lines.

Example 5 of the specification teaches the isolation of PAC clones that produce a PCR product using the D1S244 primer pair. Four clones were observed as producing an amplification product with this primer pair. Fourteen additional clones were isolated for which there was observed amplification with at least one of five of the primer pairs used in Example 4 (p. 23). The specification teaches that "The total 18 clones obtained by the 1st screening are believed to retain the genome sequences of the deleted region of the two strains NB-1 and MASS-NB-SCH-1...," however, the specification does not address the fact that the portion of chromosome 1 amplified by D1S244 is present in both the selected clones and in the cell lines. Three contigs were constructed using the 18 isolated clones (Figure 3), and portions of the contigs were sequenced (p. 25). Additional screenings resulted in the isolation of additional clones, and finally one contig of 34 PAC clones was obtained (p. 30, Figure 5).

In example 6 of the specification, applicants state "Based on Example 4 it was judged that NB-1 and MASS-NB-SCH-1 have deletions on both chromosomes in at least the regions defined from SGC-30343 to D1S2736 of 1p36... (p. 30)." Again, the specification does not address the fact that these two cell lines both showed positive amplification products for the region amplified by D1S244, a region that is within the putative "deletion region (see Figure 5)." New primers were synthesized based on the contig data, these primers were used to amplify portions of the NB-1 and MASS-NB-SCH-1 cell lines. Primer pair dJ1028013-SP6 and primer pair dJ142A6-T7 both yielded amplification products for both cell lines (Fig. 6A, lanes 6, 7, 14, and 15). These two primer pairs are at least 400 kb apart from one another, and the

chromosomal region between them includes D1S244 which also produces an amplification product in these cell lines. Primer pair dJ371E1-SP6 and primer pair dJ587C9-SP6 both did not yield amplification products in the two cell lines (Fig. 6B, lanes 6, 7, 14, and 15). These two primer pairs amplify regions that are within 100 kb of one another at the 5' end of the contig presented in figure 5.

Example 7 of the specification teaches that a search was undertaken of the NCBI gene map database with the key word "primer D1S244." Again, this is a region that the specification teaches was present in the NB-1 and MASS-NB-SCH-1 cell lines, as is evidenced by the amplification products observed in example 4. Table 7 of the specification provides a list of EST's retrieved in the search.

Example 8 teaches the sequencing of four of the clones from the contig (see Figure 9) which applicants teach include essentially all of the deletion region, though from the figure at least 20kb of the putative deletion region is not covered by the sequenced clones, the sequences of these clones are given in the sequence listing (p. 34-35).

Example 9 shows that loss of heterozygosity (LOH) on 1p36 is correlated with other markers of poor prognosis in neuroblastoma. The specification does not set forth which part of 1p36 is assayed.

Level of Unpredictability and Level of Skill in the Art

The level of skill in the art is quite high, but the unpredictability with regard to the identification of a homozygous deletion region that is found in common in the chromosomes of cells from human neuroblastoma is also quite high. It is unpredictable, for example whether or not there is in fact a homozygous deletion region that is "in common" in human neuroblastoma

cell lines or especially primary tumors. This is highlighted by the fact that of twenty-seven human neuroblastoma cell lines tested in the instant specification, only two displayed the putative homozygous deletion described in the instant disclosure. Furthermore, due to the inconsistency in the specification with regard to the presence of D1S244, it is difficult to even understand what region Applicant observed as being homozygously deleted in the two cell lines NB-1 and MASS-NB-SCH-1, and therefore, determining even what deletion region is disclosed by applicant is unpredictable, yet alone any additional deletion regions within chromsome 1p36, as are encompassed by the claims. Furthermore, as discussed by Sidransky *et al.* and Dermer (see review of the State of the Prior Art), the correlation between tumor cell lines and actual tumor tissue is an unpredictable correlation. The instant specification does not demonstrate a homozygous deletion in any actual tumor tissue, and in fact in the tumor tissue tested in example 9, only loss of herterozygosity was observed.

This unpredictability is further supported in the teachings of the post filing date art. Ohira *et al.* (Oncogene (2000) 19, 4302-4307) teach the identification and characterization of a 500-kb homozygously deleted region in a neuroblastoma cell line. This region appears to be substantially identical to the region discussed in the instant specification, however Ohira *et al.* specifically teach that the D1S244 marker is DELETED in the NB-1 and MASS-NB-SCH-1 cell lines (they refer to the later as NB-C201; see p. 4303, Col. 1 and Figure 2). Ohira *et al.* were unable to find a homozygous deletion in 180 sampled primary tumor samples at D1S244, and teach that homozygous deletions in neuroblastoma have been uncommon (p. 4303, second column). Ohira *et al.* also teach that it is possible that the two cell lines where the homozygous deletion were observed are of the same origin. Bauer *et al.* (Genes, Chromosomes, & Cancer

31 :228-239 (2001)) analyzed 49 neuroblastomas of different stages and did not observe homozygous deletion within these tumors; likewise White *et al.* did not detect homozygous deletion at any of 46 markers mapping to 1p36.1-p36.3 in a panel of 46 neuroblastoma cell lines. These findings all together underscore the high level of unpredictability with regard to a homozygous deletion region that is "common" to human neuroblastoma cells, as is set forth in the instant claims.

Quantity of Experimentation

The quantity of experimentation required to make and use the claimed invention is high, as in order to make and use the claimed invention one would have to first establish the existence of the homozygous deletion region present in common on chromosome 1p36 of human neuroblastoma. Such an undertaking would require the screening and analysis of hundreds of thousands of samples from patients with neuroblastoma to attempt to determine the presence of a homozygous deletion on 1p36.

Conclusion

In view of these factors, namely the breadth of the claims, the state of the art, the lack of working examples demonstrating a homozygous deletion present in common in human neuroblastoma cells, and the lack of clarity of the working examples to even demonstrate a homozygous deletion present in two neuroblastoma cell lines, the high level of unpredictability in the art, and the high quantity of experimentation necessary to practice the claimed invention, it is concluded that undue experimentation would be required to practice the claimed invention, and claims 1-12 are so rejected.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Insofar as the claims can be interpreted to encompass nucleic acids, chromosomes and the like, claims read on polynucleotides that would occur in nature, untouched by the hand of man, and these claims, as broadly drawn, encompass non-statutory subject matter. This rejection may be overcome by amendment of the claims to include, for example, language clarifying that the claimed nucleic acids are intended to be isolated and/or purified nucleic acids.

Insofar as the claims can be interpreted as a statement of fact, a claim to information concerning the presence of a homozygous deletion region, the claims are drawn to non-statuatory subject matter as information does not fall into a statutory class of invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Martinsson *et al.* (European Journal of Cancer, Vol. 33, No. 12, pp. 1997-2001, 1997).

With regard to claims 1 and 6, Martinsson *et al.* teach a deletion region present in common at position 36 on the short arm of chromosome 1 of human neuroblastoma (1p36). Specifically, Martinsson *et al.* teach three different deletion regions at least in their figure 1, as well as a number of smaller deletion regions that are each deletions at particular microsattelites that are in common to multiple neuroblastoma tumor samples (Table 1). This rejection applies to claims 1-12 insofar as Martinsson *et al.* appear to teach a deletion region that is substantially identical to the claimed region, though they do not teach that it is a "homozygous" deletion region, this would be an inherent property of the region if it is in fact homozygously deleted in some neuroblastoma samples. Martinsson *et al.* teach the region.

With regard to the dependent claims, the claims are being interpreted as being open claims, that is any teaching of a deletion region comprising the recited deletion region is considered to be within the scope of the claims. With regard to 2, 3, 8, 9, and 10, the region taught by Martinsson *et al.* as region (c) in Figure 1 would comprise at least the region delineated in claim 2, because the at least the region appears to be larger than the region taught herein, and it covers a set of markers that is inclusive of those discussed in this specification. The deletion regions taught by Martinsson *et al.* are at least 25 cM and appear to encompass the approximately 500 kb deletion region taught herein (as a centimorgan generally covers about 1,000,000 base pairs). Thus, the region taught by Martinsson *et al.* is defined by at least the end points delineated in claim 2, and indeed by broader end points. Likewise, the regions would encompass that defined by a primer set within the SGC30043 and D1S2736 regions.

With regard to claims 4, 5, 7, 11, and 12, again, the deletion region taught by Martinsson *et al.* would encompass a deletion region that is deleted in cell lines NB-1 and MASS-NB-SCH-1

as this region could be as little as even on nucleotide. The instant specification is not clear as to the boundaries of the deletion region which is present in these cell lines (as is discussed in the rejections under 112 previously), but insofar as D1S244 is a deletion region within these cells (as is illustrated in the figures, see Figure 9 fore example), Martinsson *et al.* teach this deletion region in common to a number of human neuroblastoma samples (see Table 1).

14. Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiraiwa *et al.* (as cited in IDS).

Hiraiwa *et al.* teach the MASS-NB-SCH-1 cell line. Hiraiwa *et al.* teach a deletion of the 1p arm of chromosome 1 on this cell line. Thus, they teach a deletion region peresent in common which comprises the deletion at 1p36, as they teach the deletion of the entire arm of the chromosome. Further, since the homozygous deletion taught in the instant specification and delineated by the parameters set forth in claims 2, 3, 8, 9, and 10 was detected in MASS-NB-SCH-1 cells, it is considered to be an inherent property of these cells and of the isolated chromosomes taught by Hiraiwa *et al.* that they comprise this deletion region. The claims set forth herein do not distinguish from the deletion region present in the host cell versus present in isolation, and therefore the teachings of Hiraiwa *et al.* anticipate the claimed invention.

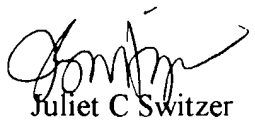
Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Juliet C Switzer
Examiner
Art Unit 1634

November 16, 2003